ARCHITECT
SYSTEM

E

CORE-M
REF 6L23
34-4426/R2

CORE-M

CUSTOMER SERVICE
UNITED STATES: 1-877-4ABBOTT

Caution: United States Federal Law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to by or on the order of a physician.

This package insert must be read carefully before product use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Key to symbols used

REF	List Number	REACTION VESSELS	Reaction Vessels
IVD	*In Vitro* Diagnostic Medical Device	SAMPLE CUPS	Sample Cups
8°C / 2°C	Store at 2-8°C	SEPTUMS	Septums
LOT	Lot Number	REPLACEMENT CAPS	Replacement Caps
	Expiration Date	SN	Serial Number
	Consult instructions for use	CONTROL NO.	Control Number
		REAGENT LOT	Reagent Lot

See **REAGENTS** section for a full explanation of symbols used in reagent component naming.

Abbott Laboratories
Diagnostics Division
Abbott Park, IL 60064 USA

Printed in USA

55

NAME

ARCHITECT CORE-M

INTENDED USE

The ARCHITECT CORE-M assay is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) in human adult and pediatric serum or plasma (dipotassium EDTA, lithium heparin, and sodium heparin) and neonatal serum. A test for IgM anti-HBc is indicated as an aid in the diagnosis of acute or recent hepatitis B virus (HBV) infection in conjunction with other laboratory results and clinical information.

Warning: Not intended for use in screening blood, plasma, or tissue donors. The effectiveness of ARCHITECT CORE-M for use in screening blood, plasma, or tissue donors has not been established.

Assay performance characteristics have not been established when the ARCHITECT CORE-M assay is used in conjunction with other manufacturers' assays for specific hepatitis markers. Users are responsible for establishing their own performance characteristics.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. The user is responsible for establishing their own assay performance characteristics in these populations.

SUMMARY AND EXPLANATION OF THE TEST

Virus specific IgM antibody has been detected in most acute viral infections and is a reliable marker for acute viral disease. High levels of IgM anti-HBc have been detected in patients with acute HBV infection[1-5] and low levels have been detected in some patients with chronic HBV infection.[7,8] Differentiation of acute and chronic HBV infection on the basis of viral markers such as HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc is difficult because most of these markers are seen during both acute and chronic disease.[1] In cases where these markers are present, acute illness with other agents such as hepatitis C, non-A, non-B, non-C hepatitis, and delta hepatitis may confuse the diagnosis.[9] Several studies have demonstrated that IgM anti-HBc is the only specific marker for the diagnosis of acute HBV infection.[2,5,10-13]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT CORE-M assay is a two-step immunoassay for the qualitative detection of IgM anti-HBc in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample is prediluted with wash buffer. The prediluted sample and anti-human IgM (mouse monoclonal) coated paramagnetic microparticles are combined. Human IgM present in the sample binds to the anti-human IgM (mouse monoclonal) coated microparticles. After washing, the anti-HBc specific IgM binds to the acridinium-labeled recombinant hepatitis B virus core antigen (rHBcAg) conjugate that is added in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A relationship exists between the amount of IgM anti-HBc in the sample and the RLUs detected by the ARCHITECT *i* optics.

The presence or absence of IgM anti-HBc in the specimen is determined by comparing the chemiluminescent signal in the reaction to the cutoff signal determined from an active ARCHITECT CORE-M calibration curve. For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Reagent Kit, 100 Tests

NOTE: Some kit sizes are not available for use on all ARCHITECT *i* Systems. Please contact your local distributor.

ARCHITECT CORE-M Reagent Kit (6L23)

- **MICROPARTICLES** 1 or 4 Bottle(s) (5.6 mL) Microparticles: Anti-human IgM (mouse monoclonal) coated microparticles in TRIS buffer with protein (1.0% bovine serum albumin and 2.5% goat IgG) additives. Minimum concentration: 0.12% solids. Preservatives: antimicrobial agents.
- **CONJUGATE** 1 or 4 Bottle(s) (5.9 mL) Conjugate: Acridinium-labeled hepatitis B virus core antigen (*E. coli*, recombinant) conjugate in succinate buffer with protein (2.5% bovine serum albumin and 2.0% bovine calf serum) additives. Minimum concentration: 0.4 µg/mL. Preservatives: antimicrobial agents.

Other Reagents

ARCHITECT *i* Pre-Trigger Solution

- **PRE-TRIGGER SOLUTION** Pre-trigger solution containing 1.32% (w/v) hydrogen peroxide.

ARCHITECT *i* Trigger Solution

- **TRIGGER SOLUTION** Trigger solution containing 0.35N sodium hydroxide.

ARCHITECT *i* Wash Buffer

- **WASH BUFFER** Wash buffer containing phosphate buffered saline solution. Preservative: antimicrobial agent.

WARNINGS AND PRECAUTIONS

For *In Vitro* Diagnostic Use.

Safety Precautions

- **CAUTION: This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens[14]. Biosafety Level 2[15] or other appropriate biosafety practices[16,17] should be used for materials that contain or are suspected of containing infectious agents.**
- For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Handling Precautions

- Do not use reagents beyond the expiration date.
- **Do not pool reagents within a reagent kit or between reagent kits.**
- Before loading the ARCHITECT CORE-M Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - **To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.**
  - **When handling microparticle vials, change gloves that have contacted human plasma/serum, since introduction of human IgM will result in a neutralized microparticle.**
  - Once a septum has been placed on the reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Storage Instructions

- The ARCHITECT CORE-M Reagent Kit must be stored at 2-8°C in an upright position and may be used immediately after removal from 2-8°C storage.
- When stored and handled as directed, the reagents are stable until the expiration date.
- The ARCHITECT CORE-M Reagent Kit may be stored on board the ARCHITECT *i* System for a maximum of 30 days. After 30 days, the reagent kit must be discarded. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.
- Reagents may be stored on or off the ARCHITECT *i* System. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** After reagents are removed from the system, initiate a scan to update the onboard stability timer.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

- The ARCHITECT CORE-M assay file must be installed on the ARCHITECT *i* System from the ARCHITECT *i* System Assay CD-ROM before performing the assay. For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.
- For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

- For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

- The following specimen tube types were verified for use with the ARCHITECT CORE-M assay:

Glass	Plastic
• Serum	• Serum • Serum separator • Lithium heparin plasma separator • Sodium heparin • Dipotassium EDTA

- The ARCHITECT *i* System does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the ARCHITECT CORE-M assay.

Specimen Conditions

- Do not use specimens with the following conditions:
  - heat-inactivated
  - pooled
  - grossly hemolyzed
  - obvious microbial contamination
- Performance has not been established for the use of cadaveric specimens or the use of body fluids other than human serum and plasma.
- **For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter.** Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- Use caution when handling patient specimens to prevent cross contamination. Use of disposable pipettes or pipette tips is recommended.
- For optimal results, inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for serum and plasma collection tubes. Gravity separation is not sufficient for specimen preparation.
- Mix thawed specimens thoroughly by low speed vortexing or by inverting 10 times. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous.
- To ensure consistency in results, specimens must be transferred to a centrifuge tube and centrifuged at > 10,000 RCF (Relative Centrifugal Force) for 10 minutes before testing if
  - they contain fibrin, red blood cells, or other particulate matter or
  - they were frozen and thawed.
- Centrifuged specimens with a lipid layer on the top must be transferred to a sample cup or secondary tube. Care must be taken to transfer only the clarified specimen without the lipemic material.
- Transfer clarified specimen to a sample cup or secondary tube for testing.

Storage

- Specimens may be stored on or off the clot, red blood cells, or separator gel for
  - up to 3 days at room temperature (study performed at 24 to 30°C) or
  - up to 7 days at 2-8°C.
- If testing will be delayed more than 3 days for specimens stored at room temperature or more than 7 days for specimens stored at 2-8°C, remove serum or plasma from the clot, red blood cells, or separator gel and store at -20°C or colder.
- Avoid more than three freeze/thaw cycles.

Shipping

- Before shipping specimens, it is recommended that specimens be removed from the clot, red blood cells, or separator gel.
- When shipping specimens, package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Specimens may be shipped ambient, at 2-8°C (wet ice), or frozen (dry ice). Do not exceed the storage time limitations listed above.

PROCEDURE

Materials Provided:

- 6L23 ARCHITECT CORE-M Reagent Kit

Materials Required but not Provided:

- ARCHITECT *i* System
- ARCHITECT *i* System Assay CD-ROM
- 6L23-01 ARCHITECT CORE-M Calibrators
- 6L23-10 ARCHITECT CORE-M Controls (or other control material)
- ARCHITECT *i* **PRE-TRIGGER SOLUTION**
- ARCHITECT *i* **TRIGGER SOLUTION**
- ARCHITECT *i* **WASH BUFFER**
- ARCHITECT *i* **REACTION VESSELS**
- ARCHITECT *i* **SAMPLE CUPS**
- ARCHITECT *i* **SEPTUMS**
- ARCHITECT *i* **REPLACEMENT CAPS**
- Pipettes or pipette tips (optional) to deliver the specified volumes.

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Assay Procedure

- Before loading the ARCHITECT CORE-M Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Handling Precautions** section of this package insert.
- Load the ARCHITECT CORE-M Reagent Kit on the ARCHITECT *i* System.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and the positive control and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
  - Use the following instructions to order a negative control (nonreactive for IgM anti-HBc):
    - Order a negative control as a patient specimen, not as a Control.
    - Manually verify the validity of the negative control every time it is run. Because the control is run as a patient specimen, a result will not be flagged by the ARCHITECT *i* System if it is outside the acceptable control range.
  - To troubleshoot control values that fall outside the control range, refer to the ARCHITECT System Operations Manual, Section 10.
- The minimum sample cup volume is calculated by the system and is printed on the Orderlist report. No more than 10 replicates may be sampled from the same sample cup. To minimize the effects of evaporation, verify adequate sample cup volume is present before running the test.
  - Priority: 64 µL for first CORE-M test plus 14 µL for each additional CORE-M test from the same sample cup.
  - ≤ 3 hours onboard: 150 µL for the first CORE-M test plus 14 µL for each additional CORE-M test from the same sample cup.
  - > 3 hours on board: Replace with a fresh sample (patient specimens, controls, and calibrators).
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare calibrators and controls.
  - ARCHITECT CORE-M Calibrators and Controls must be mixed by gentle inversion before use.
  - To obtain the recommended volume requirements for the ARCHITECT CORE-M Calibrators and Controls, hold the bottles vertically and dispense 5 drops of each calibrator or 5 drops of each control into each respective sample cup.

- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT System Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. When a laboratory requires more frequent maintenance, follow those procedures.

Specimen Dilution Procedure

- Specimens cannot be diluted for the ARCHITECT CORE-M assay.

Calibration

- To perform a calibration, test ARCHITECT CORE-M Calibrators 1 and 2 in triplicate. The calibrators should be priority loaded.
- A single sample of each control level must be tested to evaluate the assay calibration.
  - Order controls as described above.
  - Ensure that assay control values are within the ranges specified in the control package insert.
- Once an ARCHITECT CORE-M calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used.
  - Controls are out of range.

QUALITY CONTROL PROCEDURES

The ARCHITECT CORE-M Controls are in a serum matrix made from recalcified plasma. The user should provide alternate control material for plasma when necessary.

The recommended control requirement for the ARCHITECT CORE-M assay is that a single sample of each control level be tested once every 24 hours each day of use. Additional controls may be tested in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

Control values must be within the ranges specified in the control package insert. If a control result is out of its specified range, any test results generated since the last acceptable control results must be evaluated to determine if test results may have been adversely affected. Adversely affected test results are invalid, and these samples must be retested. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

RESULTS

Calculation

- The ARCHITECT *i* System calculates the cutoff RLU from the mean chemiluminescent signal of three CORE-M Calibrator 1 and Calibrator 2 replicates and stores the result.

  Cutoff RLU = [(Calibrator 2 Mean RLU - Calibrator 1 Mean RLU) x 0.75] + Calibrator 1 Mean RLU
- The ARCHITECT *i* System calculates the S/CO result for each specimen and control as follows:

  S/CO = Sample RLU/Cutoff RLU ratio

Flags

- Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

Interpretation of Results

Initial Result (S/CO)	Instrument Interpretation	Interpretation
< 0.80	NONREACTIVE (NR)	IgM anti-HBc not detected. Does not exclude the possibility of exposure to or infection with HBV. No retest required.
0.80 to < 1.21	GRAYZONE (GZ)	Antibodies to IgM anti-HBc may or may not be present. Patients with specimens exhibiting grayzone test results should be retested at approximately one-week intervals.*
≥ 1.21	REACTIVE (R)	Presumptive evidence of IgM anti-HBc. No retest required.

* Monitoring the level of IgM anti-HBc by retesting at approximately one week intervals will distinguish rapidly rising IgM anti-HBc levels associated with early acute hepatitis B infection from gradually decreasing or unchanging IgM anti-HBc levels often associated with late acute stage of HBV infection, six to nine months from the appearance of HBsAg.

LIMITATIONS OF THE PROCEDURE

- Current methods for the detection of IgM anti-HBc may not detect all infected individuals. A nonreactive test result does not exclude the possibility of exposure to or infection with HBV.
- The ARCHITECT CORE-M assay is limited to the detection of IgM anti-HBc in human serum or plasma. It can be used to determine whether a patient has, or has recently had, acute or subclinical hepatitis B infection. Supportive clinical information, including other hepatitis B markers, should also be evaluated. The test cannot determine a patient's immune status to hepatitis B.
- Specimens from patients with high levels of IgM (*e.g.*, specimens from patients with multiple myeloma) may show depressed values when tested with assay kits (such as ARCHITECT CORE-M) that use reagents containing anti-human IgM.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA).[16,18] Such specimens may show either falsely elevated or depressed values when tested with assay kits (such as ARCHITECT CORE-M) that employ mouse monoclonal antibodies.[18]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[20] Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis.
- Refer to the **SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS** section of this package insert for specimen limitations.

EXPECTED RESULTS

Due to geographic locations or demographics, assay results obtained in individual laboratories may vary from data presented.

Of the 2,059 prospectively-collected specimens tested in the ARCHITECT CORE-M clinical study, 1,207 were from individuals living in the United States with increased risk of HBV infection. All 1,207 were at risk for HBV due to lifestyle, behavior, occupation, or a known exposure event but were asymptomatic and reported no current signs or symptoms of hepatitis. Testing of these specimens was performed at three clinical sites located in Galveston, TX; Hershey, PA; and Milwaukee, WI.

The increased risk population (n=1,207) consisted of the following race/ethnic groups:

- 582 (48.22%) Caucasian
- 396 (32.81%) African-American
- 176 (14.58%) Hispanic
- 26 (2.15%) Asian
- 4 (0.33%) American Indian/Alaska Native
- 21 (1.74%) Other
- 2 (0.17%) Unknown

The 1,207 specimens from the increased risk population were obtained from the following collection locations:

- 417 (34.55%) from Galveston, TX
- 234 (19.39%) from St. Petersburg, FL
- 168 (13.92%) from Dallas, TX
- 121 (10.02%) from Plymouth, MA
- 107 (8.86%) from Miami, FL
- 47 (3.89%) from Chicago, IL
- 45 (3.73%) from Denver, CO
- 34 (2.82%) from Colton, CA
- 34 (2.82%) from High Point, NC

A total of 20 (1.66%) specimens in the increased risk population were reactive in the ARCHITECT CORE-M assay. The number of ARCHITECT CORE-M reactive results observed for the increased risk population at each collection location was:

- 5 (1.20%) from Galveston, TX
- 7 (2.99%) from St. Petersburg, FL
- 2 (1.19%) from Dallas, TX
- 2 (1.65%) from Plymouth, MA
- 1 (0.93%) from Miami, FL
- 3 (6.38%) from Chicago, IL
- 0 (0.00%) from Denver, CO
- 0 (0.00%) from Colton, CA
- 0 (0.00%) from High Point, NC

Of the 1,207 specimens, 645 (53.44%) were female and 562 (46.56%) were male. The age was not reported for one specimen. Of the remaining 1,206 specimens, the mean age was 39 years (age range: 17 to 82 years). The distribution of ARCHITECT CORE-M reactive, grayzone, and nonreactive results among the increased risk population by age and gender (n=1,207) is summarized in the following table.

		ARCHITECT CORE-M Result			
Age Group (years)	Gender	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Total
10-19	F	0 (0.00)	0 (0.00)	14 (100.00)	14
	M	0 (0.00)	0 (0.00)	7 (100.00)	7
20-29	F	4 (2.00)	1 (0.50)	195 (97.50)	200
	M	2 (1.72)	1 (0.86)	113 (97.41)	116
30-39	F	3 (2.00)	0 (0.00)	147 (98.00)	150
	M	1 (0.66)	1 (0.66)	149 (98.68)	151
40-49	F	3 (1.92)	2 (1.28)	151 (96.79)	156
	M	2 (1.15)	1 (0.57)	171 (98.28)	174
50-59	F	2 (2.06)	0 (0.00)	95 (97.94)	97
	M	1 (1.11)	1 (1.11)	88 (97.78)	90
60-69	F	2 (8.33)	0 (0.00)	22 (91.67)	24
	M	0 (0.00)	0 (0.00)	15 (100.00)	15
70-79	F	0 (0.00)	0 (0.00)	1 (100.00)	1
	M	0 (0.00)	0 (0.00)	8 (100.00)	8
80-89	F	0 (0.00)	0 (0.00)	3 (100.00)	3
	M	0 (0.00)	0 (0.00)	0 (0.00)	0
Unknown	F	0 (0.00)	0 (0.00)	0 (0.00)	0
	M	0 (0.00)	0 (0.00)	1 (100.00)	1
Total		20 (1.66)	7 (0.58)	1180 (97.76)	1207

SPECIFIC PERFORMANCE CHARACTERISTICS

Assay results obtained in individual laboratories may vary from data presented.

Precision

The ARCHITECT CORE-M assay is designed to have a Total CV of ≤ 10% for the ARCHITECT CORE-M Positive Control and a low positive panel targeted to 1.20 S/CO, and less than or equal to a total SD of 0.10 S/CO for a high negative panel targeted to 0.80 S/CO.

System Reproducibility

A five-day precision study was performed for the ARCHITECT CORE-M assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) document EP15-A2.[31] Testing was conducted at three clinical sites using three lots each of ARCHITECT CORE-M Reagents, Calibrators, and Controls per site. Two levels of controls and panels were assayed in replicates of four at two separate times of day for 5 days. The data are summarized in the following table.

			Within-Run		Within-Day		Within-Laboratory Precision (Total)		Precision with Additional Component of Between-Site*		Precision with Additional Component of Between-Lot*		Precision with Additional Components of Site and Lot (Overall)*	
Sample	n	Grand Mean S/CO	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Positive Control	360	3.19	0.115	3.6	0.115	3.6	0.121	3.8	0.160	5.0	0.163	5.1	0.187	5.8
Low Positive Panel	360	1.21	0.049	4.0	0.049	4.1	0.051	4.2	0.061	5.1	0.072	5.9	0.078	6.5
High Negative Panel	360	0.83	0.036	4.3	0.036	4.3	0.036	4.3	0.045	5.4	0.051	6.2	0.056	6.8
Negative Control	360	0.03	0.005	NA	0.005	NA	0.005	NA	0.005	NA	0.005	NA	0.005	NA

NA = not applicable
*Includes site-lot interaction variance component.

Within-Laboratory Precision

A 20-day precision study was performed for the ARCHITECT CORE-M assay based on guidance from the CLSI document EP5-A2.[32] Testing was conducted at Abbott Laboratories using three ARCHITECT CORE-M assay reagent lots, three calibrator lots, one control lot, and two instruments. Two levels of controls and panels were assayed in replicates of three at two separate times of day for 20 different days. The data are summarized in the following table.

			Mean	Within-Run		Within-Laboratory Precision (Total)	
Instrument	Sample	n	S/CO	SD	%CV	SD	%CV
1	Positive Control	360	3.20	0.127	4.0	0.137	4.3
	Low Positive Panel	359	1.21	0.049	4.0	0.052	4.3
	High Negative Panel	359	0.83	0.032	3.9	0.035	4.2
	Negative Control	360	0.04	0.005	NA	0.005	NA
2	Positive Control	360	3.13	0.131	4.2	0.141	4.5
	Low Positive Panel	358	1.18	0.052	4.4	0.057	4.8
	High Negative Panel	359	0.80	0.035	4.4	0.040	5.0
	Negative Control	356	0.03	0.005	NA	0.005	NA

NA = not applicable

59

Clinical Performance

A prospective multi-center study was conducted to evaluate the ability of the ARCHITECT CORE-M assay to detect IgM anti-HBc antibodies in a group of individuals that would normally be tested in a clinical situation. Of the 2,159 specimens tested in the ARCHITECT CORE-M clinical study, 1,207 specimens were obtained from individuals living in the United States with increased risk of HBV infection due to lifestyle, behavior, occupation, disease state, or a known exposure event, and 545 specimens were obtained from individuals living in the United States exhibiting signs and symptoms of hepatitis infection (Population One).

The 1,752 specimens in Population One were obtained from the following collection location:

- 458 (26.14%) from Galveston, TX
- 287 (16.38%) from St. Petersburg, FL
- 267 (15.24%) from Dallas, TX
- 228 (13.01%) from Chicago, IL
- 165 (9.42%) from Denver, CO
- 153 (8.73%) from Miami, FL
- 124 (7.08%) from Plymouth, MA
- 36 (2.05%) from Colton, CA
- 34 (1.94%) from High Point, NC

Population One (n=1,752) consisted of the following race/ethnic groups:

- 855 (48.80%) Caucasian
- 526 (30.02%) African-American
- 293 (16.72%) Hispanic
- 45 (2.57%) Asian
- 5 (0.29%) American Indian/Alaska Native
- 26 (1.48%) Other
- 2 (0.11%) Unknown

Of the 1,752 specimens in Population One, 872 (49.77%) were female and 880 (50.23%) were male. The age was not reported for one specimen. Of the remaining 1,751 specimens, the mean age was 42 years (age range: 17 to 83 years).

Specimens were also prospectively collected in Vietnam from 94 individuals at increased risk of HBV infection and 183 individuals with signs and symptoms of hepatitis infection (Population Two). The 277 specimens in Population Two were 100.00% Vietnamese, and 153 (55.23%) were female and 124 (44.77%) were male. The mean age was 36 years (age range: 18 to 68 years).

Each specimen was tested using a comparator IgM anti-HBc assay and three HBV reference assays, each detecting a unique serological marker (HBsAg, total anti-HBc, and anti-HBs). The HBV classification was determined for each specimen based on the reactivity patterns of the four HBV serological marker results. The comparator and reference assays were from a single manufacturer and during the clinical study, all comparator and reference testing was performed following manufacturer's instructions. Each specimen was also tested at one of three clinical sites located in Galveston, TX; Hershey, PA; or Milwaukee, WI using the ARCHITECT CORE-M assay.

Results by Specimen Classification

Following testing with the comparator IgM anti-HBc assay and the three reference HBV assays, Population One specimens were assigned an HBV classification using the reactive (+) and nonreactive (-) patterns. There were 17 unique reference marker patterns observed in the ARCHITECT CORE-M clinical study for Population One.

	HBV Reference Markers				HBV Classification
n	HBsAg	IgM Anti-HBc	Total Anti-HBc	Anti-HBs	
8	-	-	-	-	Early Acute
17	+	+	+	-	Acute
1	+	+	+	I	Chronic
2	+	-	+	+	Chronic
51	+	-	+	-	Chronic
3	+	-	-	+	Chronic
7	-	+	+	+	Recovering Acute
2	-	+	+	-	Recovering Acute/Undetectable HBsAg
220	-	-	+	+	Immune Due to Natural Infection
34	-	-	+	I	Distantly Immune/Anti-HBs Unknown
107	-	-	+	-	Distantly Immune/Anti-HBs Not Detected
351	-	-	-	+	Immune Due to HBV Vaccination
897	-	-	-	-	Susceptible
1	+	+	+	+	Late Acute/Recovering
3	+	-	+	I	Chronic
3	-	+	+	I	Early Recovery
45	-	-	-	I	Unknown
1752					Total

I = Indeterminate

Following testing with the comparator IgM anti-HBc assay and the three reference HBV assays, Population Two specimens were assigned an HBV classification using the reactive (+) and nonreactive (-) patterns. There were 10 unique reference marker patterns observed in the ARCHITECT CORE-M clinical study for Population Two.

	HBV Reference Markers				
n	HBsAg	IgM Anti-HBc	Total Anti-HBc	Anti-HBs	HBV Classification
1	+	–	–	–	Early Acute
3	+	–	+	+	Chronic
107	+	–	+	–	Chronic
1	+	–	–	+	Chronic
67	–	–	+	+	Immune Due to Natural Infection
5	–	–	+	I	Distantly Immune/Anti-HBs Unknown
12	–	–	+	–	Distantly Immune/Anti-HBs Not Detected
41	–	–	–	+	Immune Due to HBV Vaccination
37	–	–	–	–	Susceptible
3	+	–	+	I	Chronic
277					Total

I = Indeterminate

Comparison of Results

The following table compares the ARCHITECT CORE-M assay results with comparator IgM anti-HBc assay results for each of the HBV classifications for Population One. The data are summarized in the following table.

	IgM Anti-HBc Comparator						
	Reactive			Negative			
	ARCHITECT CORE-M Interpretation			ARCHITECT CORE-M Interpretation			
HBV Classification	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Total
Early Acute	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	8 (0.46)	8 (0.46)
Acute	16 (0.91)	1[a] (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	17 (0.97)
Chronic	1 (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	4[d] (0.23)	55 (3.14)	60 (3.42)
Recovering Acute	7 (0.40)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.40)
Recovering Acute/Undetectable HBsAg	2 (0.11)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.11)
Immune Due to Natural Infection	0 (0.00)	0 (0.00)	0 (0.00)	14[b] (0.80)	5[e] (0.29)	201 (11.47)	220 (12.56)
Distantly Immune/Anti-HBs Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1[f] (0.06)	33 (1.88)	34 (1.94)
Distantly Immune/Anti-HBs Not Detected	0 (0.00)	0 (0.00)	0 (0.00)	2[c] (0.11)	1[f] (0.06)	104 (5.94)	107 (6.11)
Immune Due to HBV Vaccination	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	351 (20.03)	351 (20.03)
Susceptible	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	897 (51.20)	897 (51.20)
Late Acute/Recovering	1 (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.06)
Early Recovery	3 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.17)
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	45 (2.57)	45 (2.57)
Total	**30 (1.71)**	**1 (0.06)**	**0 (0.00)**	**16 (0.91)**	**11 (0.63)**	**1694 (96.69)**	**1752 (100.00)**

[a] This specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay.

[b] Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and nonreactive by a second FDA-approved IgM anti-HBc assay. Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and grayzone by a second FDA approved IgM anti-HBc assay. Four specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. Five specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg, anti-HBe, and HBV DNA; and grayzone by a second FDA-approved IgM anti-HBc assay.

[c] One specimen was tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg, anti-HBe, and HBV DNA; and grayzone by a second FDA-approved IgM anti-HBc assay.

[d] Two specimens were tested and determined to be negative for HBeAg; positive for anti-HBe and HBV DNA; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay.

[e] Four specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay. One specimen was tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay.

[f] These specimens were tested and determined to be negative for HBeAg and HBV DNA; positive for anti-HBe; and nonreactive by a second FDA-approved IgM anti-HBc assay.

The following table compares the ARCHITECT CORE-M assay results with comparator IgM anti-HBc assay results for each of the HBV classifications for Population Two. The data are summarized in the following table.

	IgM Anti-HBc Comparator						
	Reactive			Negative			
	ARCHITECT CORE-M Interpretation			ARCHITECT CORE-M Interpretation			
HBV Classification	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Total
Early Acute	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.36)	1 (0.36)
Chronic	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1* (0.36)	113 (40.79)	114 (41.16)
Immune Due to Natural Infection	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	67 (24.19)	67 (24.19)
Distantly Immune/Anti-HBs Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (1.81)	5 (1.81)
Distantly Immune/Anti-HBs Not Detected	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	12 (4.33)	12 (4.33)
Immune Due to HBV Vaccination	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	41 (14.80)	41 (14.80)
Susceptible	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	37 (13.36)	37 (13.36)
Total	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**1 (0.36)**	**276 (99.64)**	**277 (100.00)**

* This specimen was tested and determined to be positive for HBeAg and HBV DNA; negative for anti-HBe; and grayzone by a second FDA-approved IgM anti-HBc assay.

Percent Agreement

The table below summarizes the percent agreement between ARCHITECT CORE-M and the comparator IgM anti-HBc assay for Population One by HBV classification.

HBV Classification	Positive Percent Agreement %	95% Confidence Interval	Negative Percent Agreement %	95% Confidence Interval
Early Acute	NA	NA	100.00 (8/8)	63.06 - 100.00
Acute	94.12 (16/17)	71.31 - 99.85	NA	NA
Chronic	100.00 (1/1)	2.50 - 100.00	93.22 (55/59)	83.54 - 98.12
Recovering Acute	100.00 (7/7)	59.04 - 100.00	NA	NA
Recovering Acute/Undetectable HBsAg	100.00 (2/2)	15.81 - 100.00	NA	NA
Immune Due to Natural Infection	NA	NA	91.36 (201/220)	86.84 - 94.72
Distantly Immune/Anti-HBs Unknown	NA	NA	97.06 (33/34)	84.67 - 99.93
Distantly Immune/Anti-HBs Not Detected	NA	NA	97.20 (104/107)	92.02 - 99.42
Immune Due to HBV Vaccination	NA	NA	100.00 (351/351)	98.95 - 100.00
Susceptible	NA	NA	100.00 (897/897)	99.59 - 100.00
Late Acute/Recovering	100.00 (1/1)	2.50 - 100.00	NA	NA
Early Recovery	100.00 (3/3)	29.24 - 100.00	NA	NA
Unknown	NA	NA	100.00 (45/45)	92.13 - 100.00
Total	**96.77 (30/31)**	**83.30 - 99.92**	**98.43 (1694/1721)**	**97.73 - 98.96**

NA = not applicable

Positive percent agreement = [No. of ARCHITECT CORE-M reactive results in agreement with the comparator IgM anti-HBc reactive results] / [Total number of comparator IgM anti-HBc reactive results] x 100%

Negative percent agreement = [No. of ARCHITECT CORE-M nonreactive results in agreement with the comparator IgM anti-HBc negative results] / [Total number of comparator IgM anti-HBc negative results] x 100%

The table below summarizes the percent agreement between ARCHITECT CORE-M and the comparator IgM anti-HBc assay for Population Two by HBV classification.

HBV Classification	Positive Percent Agreement %	95% Confidence Interval	Negative Percent Agreement %	95% Confidence Interval
Early Acute	NA	NA	100.00 (1/1)	2.50 - 100.00
Chronic	NA	NA	99.12 (113/114)	95.21 - 99.98
Immune Due to Natural Infection	NA	NA	100.00 (67/67)	94.64 - 100.00
Distantly Immune/Anti-HBs Unknown	NA	NA	100.00 (5/5)	47.82 - 100.00
Distantly Immune/Anti-HBs Not Detected	NA	NA	100.00 (12/12)	73.54 - 100.00
Immune Due to HBV Vaccination	NA	NA	100.00 (41/41)	91.40 - 100.00
Susceptible	NA	NA	100.00 (37/37)	90.51 - 100.00
Total	**NA**	**NA**	**99.64 (276/277)**	**98.01 - 99.99**

NA = not applicable

Negative percent agreement = [No. of ARCHITECT CORE-M nonreactive results in agreement with the comparator IgM anti-HBc negative results] / [Total number of comparator IgM anti-HBc negative results] x 100%

Percent of Positive Specimens and Percent Agreement for Individuals Diagnosed with Acute HBV Infection and Pre-Selected IgM Anti-HBc Positive Specimens

The performance of the ARCHITECT CORE-M assay was evaluated by testing prospectively-collected specimens from 14 individuals diagnosed with acute HBV infection and 16 pre-selected IgM anti-HBc positive specimens. Acute status was defined for the 30 specimens by the four HBV serological marker results. The percent of positive ARCHITECT CORE-M specimens for individuals with documented acute HBV infection was 100.00% (14/14, with a 95% confidence interval of 76.84% to 100.00%). The percent of positive ARCHITECT CORE-M specimens for the pre-selected IgM anti-HBc positive specimens was 100.00% (16/16, with a 95% confidence interval of 79.41% to 100.00%).

For individuals diagnosed with acute HBV infection and for the pre-selected IgM anti-HBc positive specimens combined, the positive percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (30/30, with a 95% confidence interval of 88.43% to 100.00%).

Clinical Performance in a Pediatric Population

The performance of the ARCHITECT CORE-M assay in a pediatric population was evaluated by testing 100 surplus specimens from a pediatric population collected in Fall River, MA by a specimen vendor, and from the 125 prospectively-collected pediatric specimens from Population One (n = 81), Population Two (n = 36), and pre-selected IgM anti-HBc positive specimens (n = 8).

For the surplus pediatric specimens, the negative percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (100/100, with a 95% confidence interval of 96.38% to 100.00%). The distribution of the ARCHITECT CORE-M reactive, grayzone, and nonreactive results for the surplus pediatric population is summarized by age and gender in the following table.

		ARCHITECT CORE-M Result			
Age Group (years)	Gender	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Total
2-12	F	0 (0.00)	0 (0.00)	25 (100.00)	25
	M	0 (0.00)	0 (0.00)	25 (100.00)	25
13-18	F	0 (0.00)	0 (0.00)	32 (100.00)	32
	M	0 (0.00)	0 (0.00)	18 (100.00)	18
Total		0 (0.00)	0 (0.00)	100 (100.00)	100

For the prospectively-collected pediatric specimens (Population One [n = 81], Population Two [n = 36], and pre-selected IgM anti-HBc positive specimens [n = 8]), the positive percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 100.00% (8/8, with a 95% confidence interval of 63.06% to 100.00%) and the negative percent agreement between the ARCHITECT CORE-M assay results and the comparator IgM anti-HBc assay results was 99.15% (116/117, with a 95% confidence interval of 95.33% to 99.98%). The distribution of the ARCHITECT CORE-M reactive, grayzone, and nonreactive results for the prospectively-collected pediatric population is summarized by age and gender in the following table.

		ARCHITECT CORE-M Result			
Age Group (years)	Gender	Reactive n (%)	Grayzone n (%)	Nonreactive n (%)	Total
2-12	F	0 (0.00)	0 (0.00)	0 (0.00)	0
	M	1 (100.00)	0 (0.00)	0 (0.00)	1
13-18	F	1 (14.29)	0 (0.00)	6 (85.71)	7
	M	1 (16.67)	0 (0.00)	5 (83.33)	6
19-21	F	1 (1.54)	0 (0.00)	64 (98.46)	65
	M	5 (10.87)	0 (0.00)	41 (89.13)	46
Total		9 (7.20)	0 (0.00)	116 (92.80)	125

Analytical Specificity

The ARCHITECT CORE-M assay was evaluated for potential cross-reactivity for specimens from individuals with medical conditions unrelated to HBV infection. The specimens were tested using the ARCHITECT CORE-M assay and the comparator IgM anti-HBc assay. The final results for each of the specimens were compared between the two assays. The data are summarized in the following table.

Reactivity of the ARCHITECT CORE-M Assay in Individuals with Medical Conditions Unrelated to HBV Infection

		Comparator IgM Anti-HBc Assay					
		Nonreactive			Reactive		
		ARCHITECT CORE-M			ARCHITECT CORE-M		
Category	n	NR[a]	GZ[a]	R[a]	NR[a]	GZ[a]	R[a]
Anti-nuclear antibody (ANA)	10	10	0	0	0	0	0
Cytomegalovirus (anti-CMV positive)	10	10	0	0	0	0	0
Elevated IgG	10	10	0	0	0	0	0
Elevated IgM	5	5	0	0	0	0	0
Epstein-Barr Virus (anti-EBV positive)	10	10	0	0	0	0	0
HBV vaccine recipient	8	8	0	0	0	0	0
Hepatitis A Virus (anti-HAV IgM positive)	10	10	0	0	0	0	0
Hepatitis C Virus (anti-HCV positive)	10	10	0	0	0	0	0
Herpes Simplex Virus (anti-HSV positive) IgG	4	4	0	0	0	0	0
Human Anti-Mouse Antibodies (HAMA) positive	7	7	0	0	0	0	0
Human Immunodeficiency Virus (anti-HIV-1 positive)	10	10	0	0	0	0	0
Human Immunodeficiency Virus (anti-HIV-2 positive)	10	10	0	0	0	0	0
Influenza vaccine recipient	10	10	0	0	0	0	0
Multiparous female	10	10	0	0	0	0	0
Multiple myeloma	2	2	0	0	0	0	0
Mumps virus	10	10	0	0	0	0	0
Non-Hodgkin's lymphoma	6	6	0	0	0	0	0
Non-viral liver disease	12	12	0	0	0	0	0
Rheumatoid factor positive	10	9	0	0	1[b]	0	0
Rubella	10	10	0	0	0	0	0
Rubeola virus	9	9	0	0	0	0	0
Syphilis	10	10	0	0	0	0	0
Systemic Lupus Erythematosus (SLE)	9	9	0	0	0	0	0
Toxoplasmosis IgG positive	9	9	0	0	0	0	0
Varicella Zoster Virus (anti-VZV positive)	4	4	0	0	0	0	0
Yeast infection	7	7	0	0	0	0	0
Total	222	221	0	0	1	0	0

[a] NR = Nonreactive, GZ= Grayzone, R = Reactive

[b] This specimen was tested and determined to be reactive for HBsAg, but did not confirm; negative for total anti-HBc; and positive for anti-HBs. A second FDA-approved IgM anti-HBc assay was performed and the specimen was determined to be negative.

Interference

At the concentrations listed below, bilirubin (conjugated and unconjugated), hemoglobin, total protein, and triglycerides showed less than 10% interference in the ARCHITECT CORE-M assay for high negative samples (S/CO range: 0.60 to 0.99) and low positive samples (S/CO range: 1.00 to 1.40):

- Bilirubin ≤ 20 mg/dL
- Hemoglobin ≤ 500 mg/dL
- Total Protein ≤ 12 g/dL
- Triglycerides ≤ 3000 mg/dL

Tube Type Matrix Comparison

The following tube types are acceptable for use with the ARCHITECT CORE-M assay:

- Glass: serum
- Plastic: serum, serum separator, lithium heparin plasma separator, sodium heparin, and dipotassium EDTA

On average, the tube types evaluated showed less than a 10% difference when compared to the control tube type (plastic serum). The distribution of the percent differences per tube type is listed in the following table.

	Distribution of Absolute Percent Differences		
Tube Type	< 10%	≥ 10% to ≤ 20%	> 20%
Glass Serum	87.8% (36/41)	12.2% (5/41)	0.0% (0/41)
Plastic Serum Separator	82.9% (34/41)	14.6% (6/41)	2.4% (1/41)
Plastic Dipotassium EDTA	80.5% (33/41)	17.1% (7/41)	2.4% (1/41)
Plastic Sodium Heparin	82.9% (34/41)	14.6% (6/41)	2.4% (1/41)
Plastic Lithium Heparin Plasma Separator	80.5% (33/41)	17.1% (7/41)	2.4% (1/41)

Seroconversion Panels

The ability of the ARCHITECT CORE-M assay to detect IgM anti-HBc was evaluated by testing eight seroconversion panels obtained from two commercial vendors.

The results were compared to the results of an FDA-approved IgM anti-HBc assay (reference). IgM anti-HBc was detected by ARCHITECT CORE-M coincident with the reference IgM anti-HBc assay in eight panels.

The profiles of the eight seroconversion panels were characteristic of an acute HBV infection progressing to eventual recovery and immunity to HBV. ARCHITECT CORE-M detected IgM anti-HBc following detection of HBsAg in all panels during the acute stage of the disease.

IgM anti-HBc remained detectable over a range of two to ten months in the eight panels. The overall ARCHITECT CORE-M results were consistent with the known serological profile of each panel.

Neonate Serum

A study was conducted to evaluate whether neonate samples may be tested with the ARCHITECT CORE-M assay. Cord blood serum was used as a surrogate for neonate serum. Twenty-one matched cord blood and maternal serum samples were spiked with IgM anti-HBc positive stock to yield a high negative sample (target S/CO 0.80) and a low positive sample (target S/CO 1.20). None of the samples were initially reactive. The data obtained upon spiking are summarized in the following table, showing the amount of bias for the cord blood serum samples from the matched maternal serum samples. For cord blood serum samples with ≥ 10% bias, one sample exhibited negative bias and the remaining samples exhibited positive bias when compared to the matched maternal serum samples.

	Distribution of % Bias			
Analyte Level S/CO	< 10%	≥ 10% to < 20%	≥ 20% to < 30%	≥ 30%
0.80	66.7% (14/21)	28.6% (6/21)	4.8% (1/21)	0.0% (0/21)
1.20	52.4% (11/21)	38.1% (8/21)	9.5% (2/21)	0.0% (0/21)

BIBLIOGRAPHY

1. Overby LR, Ling C-M, Decker RH, *et al.* Serodiagnostic profiles of viral hepatitis. In: Szmuness W, Alter HJ, Maynard JE, editors. *Viral Hepatitis.* Philadelphia, PA: Franklin Institute Press, 1981:169-182.
2. Kryger P, Aldershvile J, Mathiesen LR, *et al.* Acute type B hepatitis among HBsAg negative patients detected by anti-HBc IgM. *Hepatology* 1982;2(1):50-53.
3. Mortimer PP, Vandervelde EM, Parry JV, *et al.* The anti-HBc IgM response in the acute and convalescent phases of acute hepatitis. *J Infect* 1981;3: 339-347.
4. Lemon SM, Gates NL, Simms TE, *et al.* IgM antibody to hepatitis B core antigen as a diagnostic parameter of acute infection with hepatitis B virus. *J Infect Dis* 1981;143(6):803-809.
5. Chau KH, Hargie MP, Decker RH, *et al.* Serodiagnosis of recent hepatitis B infection by IgM class anti-HBc. *Hepatology* 1983;3(2):142-149.
6. Hoofnagle JH, Ponzetto A, Mathiesen LR, *et al.* Serological diagnosis of acute viral hepatitis. *Dig Dis Sci* 1985;30(11):1022-1027.
7. Sjogren M, Hoofnagle JH. Immunoglobulin M antibody to hepatitis B core antigen in patients with chronic type B hepatitis. *Gastroenterology* 1985;89: 252-258.
8. Surrenti C, Ambu S, Patussi V, *et al.* Diagnostic significance of anti-HBc IgM (RIA) in healthy HBsAg carriers and in chronic hepatitis B. *J Med Virol* 1986;18:229-234.
9. Perrillo RP, Chau KH, Overby LR, *et al.* Anti-hepatitis B core immunoglobulin M in the serologic evaluation of hepatitis B virus infection and simultaneous infection with type B, delta agent, and non-A, non-B viruses. *Gastroenterology* 1983;85:163-167.
10. Hawkes RA, Boughton CR, Ferguson V, *et al.* Use of immunoglobulin M antibody to hepatitis B core antigen in diagnosis of viral hepatitis. *J Clin Microbiol* 1980;11(6):581-583.
11. Roggendorf M, Deinhardt F, Frösner GG, *et al.* Immunoglobulin M antibodies to hepatitis B core antigen: Evaluation of enzyme immunoassay for diagnosis of hepatitis B virus infection. *J Clin Microbiol* 1981;13(4):618-626.
12. Kryger P. Significance of anti-HBc IgM in the differential diagnosis of viral hepatitis. *J Virol Methods* 1985;10:283-289.
13. Govindarajan S, Ashcavai M, Chau KH, *et al.* Evaluation of enzyme immunoassay for anti-HBc IgM in the diagnosis of acute hepatitis B virus infection. *Am J Clin Pathol* 1984;82(3):323-325.
14. US Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910.1030, Occupational exposure to bloodborne pathogens.
15. US Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories.* 5th ed. Washington, DC: US Government Printing Office; January 2007.
16. World Health Organization. *Laboratory Biosafety Manual.* Geneva: World Health Organization; 2004.
17. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections: Approved Guideline - Third Edition.* CLSI Document M29-A3. Wayne, PA: CLSI; 2005.
18. Primus FJ, Kelley EA, Hansen HJ, *et al.* "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy. *Clin Chem* 1988;34(2):261-264.
19. Schroff RW, Foon KA, Beatty SM, *et al.* Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. *Cancer Res* 1985;45:879-885.
20. Boscato LM, Stuart MC. Heterophilic antibodies; a problem for all immunoassays. *Clin Chem* 1988;34(1):27-33.
21. Clinical and Laboratory Standards Institute. *User Verification of Performance for Precision and Trueness; Approved Guideline - Second Edition.* CLSI Document EP15-A2. Wayne, PA: CLSI; 2005.
22. Clinical and Laboratory Standards Institute. *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition.* CLSI Document EP5-A2. Wayne, PA: CLSI; 2004.

The following U.S. Patents are relevant to the ARCHITECT System or its components. There are other such patents and patent applications in the United States and worldwide.

5 468 646	5 543 524	5 545 739
5 565 570	5 669 819	5 783 699

Abbott Laboratories
Diagnostics Division
Abbott Park, IL 60064

Manufactured for
Abbott Laboratories, Abbott Park IL
by
Abbott Diagnostics International, LTD, Barceloneta, Puerto Rico
June 2007

ARCHITECT
SYSTEM

In Vitro Test
REF 6L23-10
34-4428/R2

CORE-M

Controls

Key to symbols used

REF	Test Number	LOT	Lot Number
IVD	*In Vitro* Diagnostic Medical Device		Expiration Date
2°C–8°C	Store at 2–8°C	CONTROL –	Negative Control
	CAUTION: Consult accompanying documents	CONTROL +	Positive Control
	Hepatitis B Risk		

Abbott Laboratories
Diagnostics Division
Abbott Park, IL 60064 USA

67

INTENDED USE

The ARCHITECT CORE-M Controls are used for monitoring the performance of the ARCHITECT *i* System when used for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) when using the ARCHITECT CORE-M Reagent Kit. The performance of the ARCHITECT CORE-M Controls has not been established with any other IgM anti-HBc assays.

WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use.
- **CAUTION: This product contains human sourced infectious and/or potentially infectious components. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human sourced materials should be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens[1]. Biosafety Level 2[2] or other appropriate biosafety practices[3,4] should be used for materials that contain or are suspected of containing infectious agents.**
- The negative control is nonreactive for HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, anti-HCV, and anti-HBs.
- The positive control is reactive for IgM anti-HBc and nonreactive for HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV. Plasma is tested for HBsAg and may either be nonreactive or reactive.
- All components contain methylisothiazolones, which are components of ProClin , and are classified per applicable European Community (EC) Directives as: Irritant (Xi). The following are the appropriate Risk (R) and Safety (S) phrases.

R43 May cause sensitization by skin contact.
S24 Avoid contact with skin.
S35 This material and its container must be disposed of in a safe way.
S37 Wear suitable gloves.
S46 If swallowed, seek medical advice immediately and show this container or label.

MATERIALS PROVIDED

2 Bottles (8 mL each) ARCHITECT CORE-M Controls (1 bottle of negative control and 1 bottle of positive control).

- The negative control is recalcified IgM anti-HBc negative human plasma. Preservatives: ProClin 950, ProClin 300, and other antimicrobial agents.
- The positive control is IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma. The positive control is blue and contains Acid Blue No. 9. Preservatives: ProClin 950, ProClin 300, and other antimicrobial agents.

PREPARATION AND STORAGE

- Controls are liquid ready-to-use. No preparation is required.
- When stored and handled as directed, the controls are stable until the expiration date.
- The controls must be stored at 2-8 C in an upright position and may be used immediately after removal from 2-8°C storage.
- Refer to the ARCHITECT CORE-M assay reagent package insert for the maximum on board stability requirements.

2°C
8°C
Store at 2-8°C

QUALITY CONTROL PROCEDURES

Refer to the ARCHITECT CORE-M assay reagent package insert and ARCHITECT System Operations Manual for additional information.

The recommended control requirement for the ARCHITECT CORE-M assay is that a single sample of each control level be tested once every 24 hours each day of use. Additional controls may be tested in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

PROCEDURE

- ARCHITECT CORE-M Controls must be mixed by gentle inversion before use.
- To obtain the recommended volume requirements for the ARCHITECT CORE-M Controls, hold the bottles vertically and dispense 5 drops of each control into each respective sample cup.
- For information on ordering patient specimens and the positive control and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- Use the following instructions to order an ARCHITECT CORE-M Negative Control:
  - Order the negative control as a patient sample. The negative control cannot be ordered as a Control.
  - For the negative control, do not configure or use the Westgard or Levey-Jennings software screens for quality control analysis. The use of these screens for the negative control will result in data that is not statistically valid.
  - Manual verification of the validity of the negative control is required any time the negative control is run.
  - Because the negative control is run as a patient sample, patient values will not be flagged by the ARCHITECT *i* System if a negative control is outside of its control range. Only release patient results if a valid negative control value is obtained.
- To troubleshoot control values that fall outside the control range, refer to the ARCHITECT System Operations Manual, Section 10.

EXPECTED RESULTS

The controls must fall within the following ranges:

Control	Color	Titer	Range (S/CO)
CONTROL -	Natural	N/A	< 0.25
CONTROL +	Blue	1:2	1.77 - 4.67

Note: The insert ranges for the controls are not lot specific and represent the total range of values which may be generated throughout the life of the product. It is recommended that each laboratory establish its own means and acceptable ranges which should fall within the package insert ranges. Sources of variation that can be expected include:

- Calibration
- Control lot
- Instrument
- Calibrator lot
- Reagent lot

LIMITATIONS

- Control values have not been established for assays other than the ARCHITECT CORE-M assay. If the user wishes to use this control material with other assays, it is their responsibility to establish the appropriate ranges.
- The ARCHITECT CORE-M Controls are in a serum matrix made from recalcified plasma. The user should provide alternate control material for plasma when necessary.
- The controls are not calibrators and should not be used for assay calibration.

BIBLIOGRAPHY

1. US Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910.1030, Occupational Exposure to Bloodborne Pathogens.
2. US Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories*. 5th ed. Washington, DC: US Government Printing Office; January 2007.
3. World Health Organization. *Laboratory Biosafety Manual*. Geneva: World Health Organization; 2004.
4. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline--Third Edition*. CLSI Document M29-A3. Wayne, PA: CLSI; 2005.

Abbott Laboratories
Diagnostics Division
Abbott Park IL 60064 USA

Manufactured for
Abbott Laboratories, Abbott Park IL
by
Abbott Diagnostics International, LTD. Barceloneta, Puerto Rico

June 2007

ARCHITECT SYSTEM

In Vitro Test
REF 6L23-01
34-4427/R2

CORE-M

Calibrators

Key to symbols used			
REF	List Number	LOT	Lot Number
IVD	*In Vitro* Diagnostic Medical Device		Expiration Date
2°C – 8°C	Store at 2-8°C	CAL 1	Calibrator 1
	CAUTION! Consult accompanying documents	CAL 2	Calibrator 2
	Hepatitis B Risk		

Abbott Laboratories
Diagnostics Division
Abbott Park, IL 60064 USA

INTENDED USE

The ARCHITECT CORE-M Calibrators are used for the calibration of the ARCHITECT *i* System when the system is used for the qualitative detection of IgM antibody to hepatitis B core antigen (IgM anti-HBc) using the ARCHITECT CORE-M Reagent Kit. The performance of the ARCHITECT CORE-M Calibrators has not been established with any other IgM anti-HBc assays.

PRINCIPLES OF THE PROCEDURE

The ARCHITECT *i* System calculates the cutoff Relative Light Units (RLU) from the mean chemiluminescent signal of three replicates each of calibrator 1 and calibrator 2. The acceptability of the calibration is assessed against a parameter. If the calibration is acceptable, the cutoff RLU is calculated as follows:

Cutoff RLU = [(Calibrator 2 Mean RLU - Calibrator 1 Mean RLU) x 0.75] + Calibrator 1 Mean RLU

The acceptable calibration is stored by the ARCHITECT *i* System for use with any reagent kit of that lot. The calibration should be used in conjunction with control ranges to determine the validity of the calibration.

WARNINGS AND PRECAUTIONS

- **For *In Vitro* Diagnostic Use.**
- **CAUTION: This product contains human sourced infectious and/or potentially infectious components. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human sourced materials should be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens[1]. Biosafety Level 2[2] or other appropriate biosafety practices[3,4] should be used for materials that contain or are suspected of containing infectious agents.**
- Calibrator 1 is nonreactive for HBsAg, HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, anti-HCV, and anti-HBs.
- Calibrator 2 is reactive for IgM anti-HBc and nonreactive for HIV-1 RNA or HIV-1 Ag, anti-HIV-1/HIV-2, and anti-HCV. Plasma is tested for HBsAg and may either be nonreactive or reactive.
- All components contain methylisothiazolones, which are components of ProClin®, and are classified per applicable European Community (EC) Directives as: Irritant (Xi). The following are the appropriate Risk (R) and Safety (S) phrases.

R43 May cause sensitization by skin contact.
S24 Avoid contact with skin.
S35 This material and its container must be disposed of in a safe way.
S37 Wear suitable gloves.
S46 If swallowed, seek medical advice immediately and show this container or label.

MATERIALS PROVIDED

2 Bottles (4 mL each) ARCHITECT CORE-M Calibrators (1 bottle of calibrator 1 and 1 bottle of calibrator 2).

- Calibrator 1 is recalcified IgM anti-HBc negative human plasma. Preservatives: ProClin 950, ProClin 300, and other antimicrobial agents.
- Calibrator 2 is IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma. Preservatives: ProClin 950, ProClin 300, and other antimicrobial agents.

STANDARDIZATION

Calibrator 2 is traceable to the Reference Standard of the Paul Ehrlich Institute, Langen, Germany, HBc Referenzserum IgM 84 (IgM anti-HBc).

PROCEDURE

- The calibrators are liquid ready-to-use. No preparation is required.
- When stored and handled as directed, the calibrators are stable until the expiration date.
- The calibrators must be stored at 2-8°C in an upright position and may be used immediately after removal from 2-8°C storage.
- Refer to the ARCHITECT CORE-M assay reagent package insert for the maximum on board stability requirements.

Store at 2-8°C

QUALITY CONTROL PROCEDURES

Refer to the ARCHITECT CORE-M assay reagent package insert and ARCHITECT System Operations Manual for additional information.

A single sample of each control level must be tested to evaluate the assay calibration. For information on ordering controls, refer to the ARCHITECT System Operations Manual, Section 5.

- Ensure that assay control values are within the ranges specified in the control package insert.

Once an ARCHITECT CORE-M calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used
- Controls are out of range

PROCEDURE

- ARCHITECT CORE-M Calibrators must be mixed by gentle inversion before use.
- To perform a calibration, test ARCHITECT CORE-M Calibrator 1 and Calibrator 2 in triplicate. The calibrators should be priority loaded.
- To obtain the recommended volume requirements for the ARCHITECT Calibrators, hold the bottle vertically and dispense 5 drops of each calibrator into each respective sample cup.
- For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.

BIBLIOGRAPHY

1. US Department of Labor, Occupational Safety and Health Administration. 29 CFR Part 1910.1030. Occupational Exposure to Bloodborne Pathogens.
2. US Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories*. 5th ed. Washington, DC: US Government Printing Office; January 2007.
3. World Health Organization. *Laboratory Biosafety Manual*. Geneva: World Health Organization; 2004.
4. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections: Approved Guideline—Third Edition*. CLSI Document M29-A3. Wayne, PA: CLSI; 2005.

Abbott Laboratories
Diagnostics Division
Abbott Park IL 60064 USA

Manufactured for
Abbott Laboratories, Abbott Park IL
by
Abbott Diagnostics International, LTD, Barceloneta, Puerto Rico

June 2007